entitled "Submission of Reissue Application" filed November 18, 1999. A copy of the paper accompanies this response.

The Rejection of Claims 2-8 Under 35 U.S.C. § 112, first paragraph

Claims 2-8 stand rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter not adequately described in the specification. Applicants respectfully traverse this rejection.

Whether a specification satisfies the written description requirement is a question of fact. *Tronzo v. Biomet Inc.*, 47 U.S.P.Q.2d 1829, 1832 (Fed. Cir. 1998). The "Revised Interim Guidelines for Examination of Patent Applications Under 35 U.S.C. § 112, ¶ 1" require that the Patent Office take specific steps to determine the relevant facts. 64 Fed. Reg. 71427-39, 1999. First, the Revised Interim Guidelines require a determination of what each claim "as a whole" covers. 64 Fed. Reg. 71435. Next, the entire application must be reviewed to "determine the correspondence between applicant has described as the essential identifying characteristic features of the invention, *i.e.*, what the applicant has demonstrated possession of, and what applicant has claimed." *Id.* Finally, the Patent Office must make a determination whether the written description is sufficient to inform a skilled artisan that applicants were in possession of the claimed invention as a whole at the time the application was filed. *Id.*

In rejecting claims 2-8 for lack of an adequate written description, the Office Action asserts that "the written description is not commensurate in scope with the *claims drawn to 'mutants'* comprising the full genus of any changes to the nucleic acid molecule defined by SEQ ID NO:1, *whether it be silent or expressed as an alteration to the amino acid sequence of the encoded protein*" (emphasis added). Office Action at page 3, lines 15-18. Proper application of

the law and the Revised Interim Guidelines to claims 2-8 and this specification, however, show that the written description requirement of 35 U.S.C. § 112, first paragraph is satisfied.

Claim 2 recites:

> A preparation of antibodies which specifically binds to a human APC protein which is the product of a mutant allele found in a tumor, wherein the antibodies do not specifically bind to other human proteins, and wherein *the human APC protein is a mutant form of the amino acid sequence shown in SEQ ID NOS:2 and 7*, and the mutant allele is a mutant form of the nucleotide sequence shown in SEQ ID NO:1. (emphasis added)

Claims 3-8 recite particular mutations (claim 3) or types of mutations (claims 4-8). As acknowledged in the Office Action, the mutant allele recited in each of these claims must be a mutant form of the nucleotide sequence shown in SEQ ID NO:1. In addition, each of claims 2-8 contains the additional requirement that the human APC protein must be a mutant form of the amino acid sequence shown in SEQ ID NOS:2 and 7. Thus, the mutant allele must contain a mutation that results in a mutant APC protein. Therefore, the Patent and Trademark Office's concern over silent mutations is misplaced, as such mutations are not within the scope of the claims.

In determining whether the specification sufficiently describes the subject matter of claims 2-8, it is simply not relevant to ask whether the specification describes a representative number of "the full genus of any changes to the nucleic acid molecule defined by SEQ ID NO:1, whether it be silent or expressed as an alteration to the amino acid sequence of the encoded protein," as stated in the Office Action. The presence of additional, silent mutations would not result in a mutant form of the amino acid sequence shown in SEQ ID NOS:2 and 7 and, therefore, would not affect the binding of antibodies to the human APC protein product of the mutant allele. Instead, the relevant question for determining whether the written description

requirement is met for claims 2-8 is: does the specification provide a sufficient written description of a representative number of mutant APC alleles found in tumors that result in mutant APC proteins? The following facts indicate that the specification describes a representative number of such mutant alleles.

First, the specification provides the exon structure and nucleotide sequence of the wild-type APC gene (FIGS. 7A, 7B-1, and 7B-2, SEQ ID NO:1), as well as the amino acid sequence and structural features of the wild-type APC protein predicted from the gene sequence (FIGS. 3A-3F, SEQ ID NOS:2 and 7, column 31, line 29, to column 32, line 42).

Second, the specification also discloses types of mutations that would result in altered APC proteins:

> The mutations of the APC gene can involve gross rearrangements, such as insertions and deletions. Point mutations have also been observed.
>
> * * *
>
> The alteration [of the wild-type APC gene] may be due to either rearrangements such as insertions, inversions, and deletions, or to point mutations. Deletions may be of the entire gene or only a portion of the gene.

Column 5, lines 17-20, lines 26-29.

Third, the specification teaches numerous specific mutations in the APC gene that were or would be found in tumors and that result in mutant forms of the APC protein, as recited in claims 2-8. For example, the specification teaches that the following mutations were found in tumors:

- an 800 basepair insertion between nucleotides 4424 and 5584 (column 16, lines 52-56);

- an insertion at codon 288 (CCAGT->CCCAGCCAGT) (column 19, Table IIB);
- a point mutation that results in a change from arginine (CGA) to a stop codon (TGA) in codon 331 (column 19, Table IIB);
- a mutation in codon 437 (CAA/gtaa->CAA/gcaa), resulting in a splice donor site (column 19, Table IIB); and
- a point mutation in codon 1338, resulting in a change from Gln (CAG) to a stop codon (TAG) (column 19, Table IIB).

The specification also teaches that the following germline mutations were found in the blood of patients with FAP; these mutations would, therefore, also be found in tumors of such patients:

- a C to G transversion at codon 279, resulting in a stop codon (change from TCA to TGA) (column 18, lines 39-44 and Table IIA);
- a point mutation resulting in a change from serine (TCA) to a stop codon (TGA) at codon 712 (column 18, lines 44-46; column 19, Table IIA);
- a point mutation resulting in a change from arginine (CGA) to a stop codon (TGA) at codon 301 (column 18, Table IIA);
- a point mutation resulting in a change from arginine (CGA) to cysteine (TGC) at codon 413 (column 18, Table IIA);
- a deletion mutation from CAGAG to CAG at codon 243, resulting in a splice-junction (column 19, Table IIA);
- a deletion mutation from CTTTCA to CTTCA at codon 456, resulting in a frameshift (column 19, Table IIA);
- substitution of a T by a G at codon 500, changing the normal tyrosine codon to a

stop codon (column 19, Table IIA); and

- a deletion of two adjacent nucleotides, at positions 730 and 731 in the APC cDNA sequence of SEQ ID NO:1 (column 29, lines 3-9).

Fourth, the specification extensively teaches techniques for detecting and identifying both the specific mutations disclosed and other mutations which result in altered APC protein. See, for example, column 5, line 60, to column 9, line 21.

The law requires that the specification be considered as a whole when determining whether it describes a particular invention. *In re Wright*, 9 U.S.P.Q. 1649, 1651 (Fed. Cir. 1989). Considering the specification as a whole, one of skill in the art at the time the application was filed would have understood applicants to have been in possession of mutant APC alleles that (1) are found in tumors, (2) are mutant forms of SEQ ID NO:1, and (3) result in mutant forms of the amino acid sequence shown in SEQ ID NOS:2 and 7. Therefore, the skilled artisan would have understood applicants to have been in possession of antibodies which specifically bind to such mutant APC proteins, as recited in independent claim 2. Applicants have taught mutant APC proteins generically and specifically. Surely the extensive disclosure of mutations constititues a teaching of a representative number of such APC mutant proteins.

Claim 3 recites that the mutant allele has a particular mutation selected from mutations at codons 243, 279, 288, 301, 331, 413, 437, 456, 500, 712, and 1338. As shown in the list of specific mutations, above, mutations at each of these codons are described in the specification. Similarly, each of claims 4-8 recites particular types of mutations that result in mutant forms of APC protein (premature termination, missense, frameshift, splice junction, and insertion mutations). The specification provides examples of each of these types of mutation. The Office Action's speculations regarding the presence of additional changes to the sequence of SEQ ID

NO:1 (*e.g.*, normal allelic variations which do not result in a mutant form of SEQ ID NO:2 or 7) are merely conjecture. Notwithstanding, such allelic variation would not affect the claimed subject matter. The claims are directed to antibodies that bind to mutant forms of APC proteins. The presence of additional silent allelic variations in the gene encoding the mutant APC protein would not affect the claimed antibodies. Such allelic mutations are invisible to an antibody. The specification provides a representative number of the mutant APC proteins required by claims 2-8.

As shown by the facts presented above, the specification as a whole satisfies the written description requirement of 35 U.S.C. § 112, first paragraph, for the subject matter of claims 2-8. Applicants respectfully request withdrawal of the rejection of claims 2-8 under 35 U.S.C. § 112, first paragraph.

The Rejection of Claim 1 Under 35 U.S.C. § 112, second paragraph

Claim 1 stands rejected under 35 U.S.C. § 112, second paragraph. The Office Action points out that claim 1 refers to an amino acid sequence but recites SEQ ID NO:1. SEQ ID NO:1 contains a nucleic acid sequence and an amino acid sequence. For clarity, claim 1 has been amended to delete SEQ ID NO:1. Applicants respectfully request withdrawal of the rejection.

Respectfully submitted,

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